

**REMARKS**

Claims 45-51, 53-66, 68-87, 95-98, and 102 are all the claims pending in the application.

**I. The Obviousness-Type Double Patenting Rejection**

Claims 45-51, 53-60, 70-87 and 95-96 are rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims 1-10 of U.S. Patent 6,239,113.

Specifically, the Examiner states that this rejection is maintained because there is a typographical error in the Terminal Disclaimer filed July 24, 2002, with respect to the serial number of the application which forms a basis for the double patenting rejection.

Applicants submit herewith a new Terminal Disclaimer. In view thereof, it is requested that the obviousness-type double patenting rejection over U.S. Patent No. 6,239,113 be reconsidered and withdrawn.

**II. The Rejection Under 35 U.S.C. §112, First Paragraph**

Claims 45, 47-51, 53-60, 70-81, 83-87 and 95-96 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled by the specification.

Specifically, the Examiner states that the specification is enabling for "treatment" of eye infections, but alleges that the specification does not provide

AMENDMENT UNDER 37 C.F.R. §1.116  
U.S. Appln. No. 09/767,943

enablement for “prevention” of eye infections, because “prevention” reads on treating a healthy eye.

Applicants respectfully submit that the present specification provides a fully enabling disclosure for the invention, as originally claimed, and that the disclosure would enable one of ordinary skill in the art to make and use the invention, as claimed, without undue experimentation. However, for the purposes of furthering prosecution, Applicants amend independent claims 45 and 70 to delete “or prevent”, without prejudice or disclaimer. In view thereof, it is requested that the rejection under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

**III. The Rejection Under 35 U.S.C. §112, Second Paragraph**

Claims 47-48 and 83-84 are rejected under 35 U.S.C. §112, as allegedly being indefinite.

Specifically, the Examiner states that structural Formula (I) has not been included in these claims.

Applicants amend claims 47 and 83 to include formula (I). Therefore, it is respectfully submitted that Applicants’ claims are clear and definite and it is requested that the rejection under 35 U.S.C. §112 be reconsidered and withdrawn.

**IV. The Rejections Based on WO 95/09601 and Curatolo et al**

Claims 61-66, 68-69, 97-98 and 101-102 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over WO 95/09601 or Curatolo et al.

AMENDMENT UNDER 37 C.F.R. §1.116  
U.S. Appln. No. 09/767,943

Specifically, the Examiner states that the recitation "topical ophthalmic composition" is not being given any patentable weight because the recitation occurs in the preamble.

Applicants respectfully submit that the present invention is not rendered obvious over the disclosures of WO 95/09601 or Curatolo et al and request that the Examiner reconsider and withdraw these rejections in view of the following remarks.

First of all, Applicants respectfully traverse the Examiner's rigid position that recitations in a preamble of a claim are not to be given any patentable weight. "No litmus test can be given with respect to when the introductory words of a claim, the preamble, constitute a statement of purpose for a device or are, in themselves, additional structural limitations of a claim ... The effect preamble language should be given can be resolved only on review of the entirety of the patent to gain an understanding of what the inventors actually invented and intended to encompass by the claim." Corning Glass Works v. Sumitomo Electric U.S.A. Inc., 9 USPQ2d 1962, 1966 (CA FC 1989). The Court in Corning determined that the term "an optical waveguide" in the preamble does not merely state a purpose or intended use for the claimed structure, rather, those words do give "life and meaning" and provide further positive limitations to the invention claimed. Id. at 1966.

AMENDMENT UNDER 37 C.F.R. §1.116  
U.S. Appl. No. 09/767,943

Further, the Court in Kropa v. Robie, 88 USPQ 478 (CCPA 1951), the case cited by the Examiner, stated that the meaning of the preamble may be a vital term of a count and must be taken from the application in which the counts originated. Id., at 481 (CCPA 1951). In addition, in *ex parte* cases where the preamble of the claim or count is expressly or by necessary implication given the effect of a limitation, the introductory phrase is deemed essential to point out the invention defined by the claim or count and the preamble is considered necessary to give life, meaning, and vitality to the claims or counts. Id. Specifically, the Court in Kropa stated:

[T]he words "An abrasive article" are essential to point out the invention defined by the counts. In our judgment those introductory words give life and meaning to the counts, for it is only by that phrase that it can be known that the subject matter defined by the claims is comprised as an abrasive article. Every union of substances capable *inter alia* of use as abrasive grains and a binder is not an "abrasive article." The term calls forth a distinct relationship between the proportions of grain and resin comprising the article.

Id.

By direct analogy, the term "topical ophthalmic composition" gives life and meaning to the instant composition claims, for it is only by that phrase that it can be known that the subject matter defined by the claims is comprised as a topical ophthalmic. Every union of substances capable, *inter alia*, of using an azalide antibiotic is not a "topical ophthalmic." The preamble of the claims calls for a distinct function. See, for example, Applicants' specification, pages 1-3. Further,

AMENDMENT UNDER 37 C.F.R. §1.116  
U.S. Appln. No. 09/767,943

Applicants have clearly expressly indicated that the preamble should be give the effect of a limitation.

Independent Claims 61, 65 and 102 relate to a topical ophthalmic composition. The recitation "topical ophthalmic" is clearly a limitation which gives "life and meaning" to the claims. This is because not all compositions can be topically administered ophthalmically, i.e., to the eye. For example one of ordinary skill in the art would not administer a tablet or capsule to the eye. One of ordinary skill in the art would also not administer an ingredient that is toxic or detrimental to the eye. Further, a composition that is administered to the eye is one which has a pH and osmolality which is compatible with eye tissue and the aqueous environment of the eye. Not all pHs or osmolalies are compatible , for example, an acidic pH, such as found in the stomach, would not be compatible to the eye.

Turning to the cited art, WO 95/09601 teaches a periodontal (buccal) composition. This composition is not compatible with the eye and as such, can not be used in the eye. Thus, the compositions of WO 95/09601 can not be considered topical ophthalmic compositions, as claimed in the present application.

Curatolo et al relates to an oral dosage composition. In particular, Curatolo et al relates to tablets, capsules or powders. Such compositions clearly are not used in the eye, and thus can not be considered topical ophthalmic compositions, as claimed in the present application.

AMENDMENT UNDER 37 C.F.R. §1.116  
U.S. Appln. No. 09/767,943

Applicants have amended claims 61, 65 and 102, the independent topical ophthalmic composition claims, to recite that the topical ophthalmic composition has an osmotic pressure of from 10 to 400 mOsM. Support for the amendment may be found in the specification as originally filed, for example, at page 10, lines 15-17. WO 95/09601 and Curatolo et al do not teach or disclose a topical ophthalmic composition having Applicants' claimed osmotic pressure. For the dry compositions of WO 95/09601 and Curatolo et al, osmotic pressure has no meaning without water.

Applicants have also amended claims 61, 65 and 102 to recite that the topical ophthalmic composition does not contain constituents that are physiologically or ophthalmically harmful to the eye. Support for the amendment may be found in the specification as originally filed, for example, at page 10, lines 5-7. The oral formulations disclosed by WO 95/09601 and Curatolo et al contain constituents, e.g., fillers and dyes, which are not compatible in the eye due to their toxicity and abrasion. Additionally, Applicants' composition claims each recite ranges that are below about 5% of an azalide antibiotic. Compositions containing high amounts of azalide antibiotic, such as those disclosed by WO 95/09601 and Curatolo et al, may be in forms that are physiologically or ophthalmically harmful to the eye.

Enclosed herewith is a Declaration Under 37 C.F.R. §1.132 by Dr. Lyle Bowman, one of the inventors of the present application. The Declaration establishes that the compositions and ingredients disclosed by WO 95/09601 and

AMENDMENT UNDER 37 C.F.R. §1.116  
U.S. Appl. No. 09/767,943

Curatolo et al are not compositions that one of ordinary skill in the art would consider to be topical ophthalmic compositions and contain constituents that are physiologically or ophthalmically harmful to the eye. See, for example, the discussion in the §132 Declaration of the components in Curatolo et al.

Further, claim 102 has be amended to recite that the topical ophthalmic composition is in the form of a depot which is capable of sustained release of said azalide antibiotic. While the cited art does disclose sustained release oral drug delivery systems, neither of WO 95/09601 or Curatolo et al teach or disclose a topical ophthalmic composition that is in the form of a depot. For example, the representative sustained release composition example of WO 95/09601, Example II, is in a shape capable of being inserted into subgingival cavities with pliers, which would not be suitable for insertion into an eye. Further, the composition contains propylene carbonate, which is an irritant in the eye, and a concentration of 30 wt. % azithromycin, which if released rapidly will be toxic to the eye.

For the above reasons, it is respectfully submitted that the subject matter of claims 61-66, 68-69, 97-98 and 102 is neither taught by nor made obvious from the disclosures of WO 95/09601 or Curatolo et al and it is requested that the rejections under 35 U.S.C. §103(a) be reconsidered and withdrawn.

**V. The Rejection Based on Davis et al in view of Bright et al**

Claims 45-51, 53-66, 68-87, 95-98 and 101-102 are rejected as allegedly being unpatentable over Davis et al in view of Bright et al.

Specifically, the Examiner states that since azithromycin is known to have enhanced stability in aqueous formulations over erythromycin, "as admitted by Applicants." The Examiner concludes that one skilled in the art would have been motivated to substitute azithromycin for erythromycin in the composition and method disclosed by Davis et al.

Applicants respectfully submit that the present invention is not rendered obvious over the disclosures of Davis et al and Bright et al and request that the Examiner reconsider and withdraw this rejection in view of the following remarks.

First of all, Applicants note that the Examiner's "motivation" for the rejection, the enhanced stability in aqueous formulation of azithromycin over erythromycin, is stated to be "as admitted by Applicant." However, Applicants' discussion concerning the stability of azithromycin over erythromycin relates to the exhibition of improved acid stability related to oral dosage forms. See page 5 of the present specification. Acid stability is a property desired in treatment via an oral dosage form, such as those disclosed in WO 95/09601 and Curatolo et al discussed above, because, when administered orally, the composition proceeds through the stomach, i.e. a gastric acid environment. The present invention relates to



compositions that are applied topically to the eye, and not via the stomach, which contains gastric acid and for which acid stability is important.

Contrary to the Examiner's assertions, acid stability for gastric acid environments are be predictive as property required in topical ophthalmic compositions.

Further, high cellular uptake and retention via oral administration as taught in the prior art allows for systemic delivery of azithromycin to the site of the infection. The high cellular uptake of azithromycin is thought to be due to tissue binding in cells.

Oral administration leads to systemic circulation of the drug due to the partition of the drug into the tissue. Systemic exposure to azithromycin following ocular topical application is extremely low. Oral administration also leads to phagocytic delivery. The phagocytic delivery of azithromycin, while an important factor for systemic infection treatment by oral dosing, does not play any significant role in treating ocular infection using topical administration.

From the known half-life in tissue data, one of ordinary skill in the art could not predict that azithromycin would be suitable for use in the eye by topical administration for at least the following two reasons:

- 1) The bacteria for which azithromycin is a systemically targeted are different from bacteria which cause infections in the eye. Even if some of same

AMENDMENT UNDER 37 C.F.R. §1.116  
U.S. Appl. No. 09/767,943

bacteria are found in the eye, the strains are generally different resulting in different bacterial sensitivities; and

2) Since different bacteria and strains exist in the eye, drug levels to kill or inhibit the bacteria are different. It was not known in the art if sufficient levels of azithromycin could be obtained by topical administration since systemic and topical administration result in different targeted tissue levels.

The enclosed Declaration Under 37 C.F.R. §1.132 clarifies the knowledge in the art concerning the properties of azithromycin.

Furthermore, the acid stability of an oral drug where the loading is 500mg (a typical oral dosage; see, for example, Curatolo et al) can not be used to predict stability of aqueous solutions containing Applicants' claimed concentrations (5% or less).

In addition, in oral administration, which leads to systemic circulation of the drug, azithromycin rapidly partitions into the tissue, which is different than the uptake of erythromycin. However, systemic exposure to azithromycin is low following ocular topical application to the eye.

Besides direct uptake by tissues, azithromycin may also reach the sites of infection by phagocytic delivery. Phagocytic cells, such as macrophages, monocytes, and neutrophils, can accumulate and hold azithromycin for a long period of time. This property allows these cells to carry high concentration of the drug to the site of

AMENDMENT UNDER 37 C.F.R. §1.116  
U.S. Appln. No. 09/767,943

infection upon oral administration. When these cells reach the site of infection, azithromycin could be unloaded during the process of phagocytosis. The phagocytic delivery of azithromycin, while an important factor for systemic infection treatment by oral dosing, does not play any significant role in treating ocular infection using topical administration as claimed in the present application.

Applicants respectfully submit that one of ordinary skill in the art, in view of the disclosures of Davis et al and Bright et al, would not have been motivated to substitute azithromycin for erythromycin in the composition and method disclosed by Davis et al, to make Applicants' claimed topical ophthalmic compositions or for use in Applicants' claimed processes, for the purposes of providing a composition that would have improved acid stability. That is, improved acid stability for gastric conditions would not motivate one of ordinary skill in the art to substitute azithromycin for erythromycin in a topical ophthalmic compositions or in a process for treating an eye.

The Examiner's original statement of the rejection merely confirms that azithromycin is not a novel compound (Office Action dated April 24, 2002, page 6, lines 1-4). The Examiner's stated reason for substitution of azithromycin for erythromycin is "because the results obtained by such a substitution would have been expected." Applicants' respectfully submit that the results obtained by such a substitution being "expected" is not a valid motivation for making a change to the

AMENDMENT UNDER 37 C.F.R. §1.116  
U.S. Appln. No. 09/767,943

compositions and methods disclosed in Davis et al. The question of whether there is a reasonable expectation of success, on its own, is not sufficient to establish a *prima facie* case of obviousness, there must first be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings and the prior art references must teach or suggest all of the claim recitations. See MPEP §2143.

The Examiner is clearly using hindsight to recreate Applicants' claimed invention. Hindsight has repeatedly been held to be improper and ineffective in supporting an argument of *prima facie* obviousness. See, e.g., In re Fritch, 23 USPQ2d 1780 (Fed. Cir. 1992); In re Bond, 15 USPQ2d 1556 (Fed. Cir. 1990); In re Laskowski, 10 USPQ2d 1397 (Fed. Cir. 1989). At best, the Examiner is stating that it would have been obvious to try azithromycin in topical ophthalmic compositions and methods. However, the standard of patentability is not "obvious to try." In re Fine, 5 USPQ2d 1596 (Fed. Cir. 1988). Rather, it is a higher standard. There must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant. Teachings of references can be combined only if there is some suggestion or incentive to do so. In re Lee, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002).

AMENDMENT UNDER 37 C.F.R. §1.116  
U.S. Appln. No. 09/767,943

It is respectfully submitted that, contrary to the Examiner's position, azithromycin and erythromycin are not equivalents and one of ordinary skill in the art would not have been motivated to substitute one for the other based on the teachings of Davis et al or Bright et al. It was simply not known in the art, until Applicants' invention, whether azithromycin could effectively permeate the conjunctiva of the eye upon topical dosing. The more charged a drug is, like azithromycin over erythromycin, the lower the conjunctival permeation. Thus, the knowledge in the art concerning the charge of azithromycin teaches away from Applicants' claimed invention. The knowledge in the art could not predict if sufficient tissue concentrations could be achieved comparable to erythromycin levels, without tissue binding. Thus, there clearly was no reasonable expectation of success, contrary to the Examiner's apparent contention.

Further, the Examiner's reliance on Applicants' comments concerning acid stability in gastric environments is not a motivating factor in the relevant art. Here the relevant art is topical compositions for the eye.

While, as set forth above, it is believed the Examiner has not established a *prima facie* case of obviousness, Applicants further note that the ability of the compositions of the present claims to permeate the conjunctiva upon topical dosing shows an unexpected result over the knowledge in the art.

AMENDMENT UNDER 37 C.F.R. §1.116  
U.S. Appln. No. 09/767,943

For the above reasons, it is respectfully submitted that the subject matter of claims 45-51, 53-66, 68-87, 95-98 and 102 is neither taught by nor made obvious from the disclosures of Davis et al and Bright et al, alone or in combination, and it is requested that the rejection under 35 U.S.C. §103(a) be reconsidered and withdrawn.

**VI. Conclusion**

In view of the above, Applicants respectfully submit that their claimed invention is allowable and ask that the obviousness-type double patenting rejection, the rejection under 35 U.S.C. §112 and the rejections under 35 U.S.C. §103 be reconsidered and withdrawn. Applicants respectfully submit that this case is in condition for allowance and allowance is respectfully solicited.

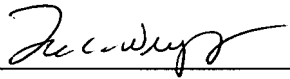
If any points remain at issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the local exchange number listed below.

AMENDMENT UNDER 37 C.F.R. §1.116  
U.S. Appln. No. 09/767,943

Applicants hereby petition for any extension of time which may be required to maintain the pendency of this case. The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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